REMARKS

Prior to the present amendment, claims 17-86 were pending. Of claims 17-86, claims 19, 21-59, 80 and 82-84 were withdrawn by the examiner as being drawn to non-elected inventions. By the present amendment, applicants have canceled claims 60-66, 69, 74-75 and 81 and amended claims 17-18, 67-68, 70-73, 76, 78, 79 and 85. Accordingly, claims 17-18, 20, 67-68, 70-73, 76-79, and 85-86 are currently pending.

In the office action, the examiner rejected claims 61-62, 65, 74-75 and 85-86 under 35 U.S.C. §112, second paragraph allegedly for indefiniteness for various reasons. Applicants have cancelled claims 61, 62, 65, and 74-75. Therefore, the rejection of claims 61-62, 65, 74-75 is now moot and should be withdrawn.

The examiner states that claims 85-86 are indefinite for omitting an essential step in the claims. The examiner contends that the omitted step is how to obtain the polynucleotide encoding polypeptide antibody specific for factor VIII. Applicants have complied with the examiner's suggestion and included in claim 85, a step which recites "providing a polynucleotide encoding said polypeptide." Accordingly, applicants respectfully request that the rejection be withdrawn. Support for the amendment can be found in the specification as originally filed. See *inter alia*, claim 8 as originally filed.

Claims 60-79 and 81 were rejected under 35 U.S.C. §112 first paragraph as allegedly containing subject matter not described in the specification. The examiner contends that claims 60-63 contain new matter.

Applicants have cancelled claims 60-63. Accordingly, the rejection is moot and should be withdrawn.

Claims 17-18, 20, 60-79, 81 and 85-86 were rejected under 35 U.S.C. §112, first paragraph allegedly for containing subject matter not described in the specification to enable one skilled in the art to make and/or use the invention.

The examiner contends that the specification does not provide SEQ ID NOs for both scFv-EL14 and scFV-IT2 recited in claims 74-75. Applicants have cancelled claims 74 and 75. Therefore, the rejection of claim 74 and 75 is moot and should be withdrawn.

The examiner further alleges that the specification is not enabled for any polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors. Specifically, the examiner contends that the specification is not enabled for any polypeptide comprising a "variable part of the heavy chain" of a human antibody with factor VIII specificity or any "part thereof" which at least includes the CDR3 as recited in claim 17. Moreover, the examiner states that the specification does not provide guidance for determining amino acids that mimick the factor VIII-binding of a CDR or any derivative of an amino acid sequence from a CDR of a human antibody. Thus, the examiner contends that the claimed invention requires undue experimentation.

Applicants have amended claim 17 to expressly state that the claimed polypeptide comprises a human antibody heavy chain variable part of a human antibody with factor VIII specificity and a human antibody light chain variable part. Thus, the claimed polypeptide no longer refers to "any CDR," "mimicking amino acids" or "derivates of amino acid sequences."

The presence of a heavy chain variable part of a human antibody with factor VIII specificity in the claimed polypeptide ensures that the claimed polypeptide possesses specific binding to factor VIII and interference with the activity of factor VIII inhibitors.

As shown in the specification, the light chain variable region is derived from a human antibody. See, for instance, Example 2 of the specification, on page 19 , lines 29-35 which state the following:

> The digested fragments were purified and dissolved in TE (10 mM Tris-CHL pH=8.0; 0.1 mM EDTA). The vector pHEN-1-VLrep has been described previously and contains a **light chain repertoire derived of two non-immunized donors**. Insertion of a heavy chain repertoire in this vector has been shown to result in the production of antibody fragments that consist of the variable domains of both heavy and light chain. *(Emphasis added.)* *(Citations omitted.)*

The heavy chain repertoire gives rise to VH domains. The light chain repertoire contains a collection of VL domains. As demonstrated in, *inter alia,* Example 2 of the specification, a clone contains both a VH and a VL domain and is expressed as a scFV on the surface of a bacteriophage or as a soluble scFv.

Moreover, the specification discloses numerous polypeptides (e.g., scFV fragments) comprising a heavy chain variable region from a human antibody with specificity for factor VIII and a light chain variable region of a human antibody. These polypeptides disclosed in the specification include, *inter alia*, svFv-EL-14 (DP-10), VHEL-14 (SEQ ID NO:23), svFv-IT-2 (DP-14), CHIT2 (SEQ ID NO:25), VH-IT2(SEQ ID NO:25), VH EL-5 (DP-14) (SEQ ID NO:27), VH EL-25 (DP-14) (SEQ ID NO:28), B38 (SEQ ID NO:32), B18 (SEQ ID NO: 34), B35 (SEQ ID NO:36), and B04 (SEQ ID NO:38).

Accordingly, the examples of polypeptides disclosed in the specification and the examples section of the specification support that the specification provides adequate disclosure to enable one skilled in the art to make and use the claimed polypeptides having the claimed

activity (e.g., specific binding to factor VIII and interference with the activity of factor VIII inhibitors).

The examiner also questions whether the claimed composition of claims 20 and 81 would function as pharmaceutical compositions. The specification provides *in vitro* data demonstrating the efficacy of the claimed invention in neutralizing the activity of factor VIII inhibitors present in plasma of patients with haemophilia. A person having ordinary skill in the art would also expect efficacy *in vivo*.

For the above reasons, applicants respectfully request that the examiner reconsider the rejection of claims 17-18, 20, 60-79, 81 and 85-86 under 35 U.S.C. §112 allegedly for lack of enablement and withdraw the rejection.

Claims 17-18, 20, 60-79, 81 and 85-86 were rejected under 35 U.S.C. §112, first paragraph allegedly for containing subject matter not described in the specification to reasonably convey to one skilled in the art that applicants, at the time the application was filed, had possession of the claimed invention.

The examiner contends that applicants are not in possession of any polypeptide capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors. Specifically, the examiner contends that applicants are not in possession of any polypeptide comprising a "variable part of the heavy chain" of a human antibody with factor VIII specificity or any "part thereof" which at least includes the CDR3 as recited in claim 17. Moreover, the examiner states that applicants are not in possession of a polypeptide containing an amino acid sequence that mimicks the factor VIII-binding of a CDR or any derivative of an amino acid sequence from a CDR of a human antibody.

As stated above, applicants have amended claim 17 to expressly define that the claimed polypeptide comprises a human antibody heavy chain variable part of a human antibody with

factor VIII specificity and a human antibody light chain variable part. Thus, the claimed polypeptide no longer refers to "any CDR," "mimicking amino acids" or "derivates of amino acid sequences."

As discussed above, the presence of a heavy chain variable part of a human antibody with factor VIII specificity in the claimed polypeptide ensures that the claimed polypeptide possesses specific binding to factor VIII and interference with the activity of factor VIII inhibitors. The light chain variable region is derived from a human antibody.

The specification also discloses numerous polypeptides comprising a heavy chain variable region from a human antibody with specificity for factor VIII and a light chain variable region of a human antibody. These polypeptides disclosed in the specification include, *inter alia*, svFv-EL-14 (DP-10), VHEL-14 (SEQ ID NO:23), svFv-IT-2 (DP-14), CHIT2 (SEQ ID NO:25), VH-IT2(SEQ ID NO:25), VH EL-5 (DP-14) (SEQ ID NO:27), VH EL-25 (DP-14) (SEQ ID NO:28), B38 (SEQ ID NO:32), B18 (SEQ ID NO: 34), B35 (SEQ ID NO:36), and B04 (SEQ ID NO:38).

Therefore, applicants at the time the application was filed, had possession of the claimed invention. Accordingly, applicants respectfully request that the examiner reconsider and withdraw the rejection of claims 17-18, 20, 60-79, 81 and 85-86 under 35 U.S.C. §112.

Claims 60-66, 70-73, 76-79 and 81 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Lenting et al. (J. Biol. Chem, 269:7150:7165, 1994). The examiner contends that Lenting et al. discloses antibody mimicks and derivatives of antibodies specific for factor VIII. Further, the examiner states that Lenting et al. discloses that the antibody CLB-CAg A effectively inhibited FIXa binding to FVIII-LC. Therefore, the examiner asserts that the claimed invention is anticipated by Lenting et al.

Applicants respectfully disagree. Lenting et al. disclosures several **murine** monoclonal antibodies directed against factor VIII. These murine monoclonal antibodies include CLB-CAg A, CLB-CAg12, CLB-CAg 69 and CLB-CAg 117 directed against factor VIII-LC and CLB-CAg 9 directed against factor VIII-HC.

However, nowhere in Lenting et al. is there any disclosure or suggestion of antibody fragments or derivatives of a **human** antibody specific for factor VIII, let alone polypeptides or scFV fragments containing a heavy chain variable part of a human antibody as in the present invention.

Further, Lenting et al. discloses that the murine monoclonal antibodies inhibit factor VIII activity by interfering with the binding of factor VIII to factor IXa. Nowhere in Lenting et al. is there any disclosure or suggestion that the murine monoclonal antibodies interfere with the binding of inhibitors of factor VIII.

In stark contrast, the claimed polypeptides interfere with the activity of **inhibitors** of factor VIII as is recited in the claimed invention.

For the reasons above, the claimed invention is not anticipated by Lenting et al. Accordingly, applicants respectfully request that the rejection of claims 60-66, 70-73, 76-79 and 81 under 35 U.S.C. §102(b) be reconsidered and withdrawn.

Claims 17-18, 20, 60-68, 71, 73, 76-79 and 81 were rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Fijnvandraat et al. (Blood, 91:2347-2352, 1998). According to the examiner, Fijnvandraat et al. discloses inhibitory antibodies derived from hemophilia A patients's plasma which are directed against factor VIII. Further, the examiner state that Fijnvandraat et al teaches that the purified IgG antibodies inhibit binding of factor IXa to immobilized factor VIII light chain. Therefore, the examiner concludes that the cited reference anticipates that claimed invention.

Applicants respectfully disagree. Fijnvandraat et al. discloses human polyclonal antibodies to factor VIII. These antibodies are antibody molecules that inhibit factor VIII activity by interfering with the binding of factor VIII to factor IXa. These antibodies are completely different from the claimed polypeptides.

The claimed polypeptides inhibit the binding of inhibitors of factor VIII. Furthermore, there is no suggestion or disclosure in Fijnvandraat et al. of antibody fragments or derivatives which inhibit activity of inhibitors of factor VIII. By contrast, the claimed polypeptides (e.g., scFv fragments) interfere with the activity of inhibitors of factor VIII. Such polypeptides are not disclosed in the prior art.

Thus, Fijnvandraat et al. does not disclose or suggest the claimed invention. Accordingly, applicants respectfully request that the rejection of claims under 35 U.S.C. §102(b) be reconsidered and withdrawn.

Claims 17-18, 20, 60-68, 71, 73, 76-79 and 81 were rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Scandella (International Journal of Pediatric Hematology/Oncology, 1:437-447, 1994). According to the examiner, Scandella discloses human alloantibodies and autoantibodies which inactivate factor VIII. Therefore, the examiner contends that the claimed invention is anticipated by Scandella.

Applicants respectfully disagree. Scandella discloses human polyclonal antibodies which inhibit factor VIII activity by interfering with the binding of factor VIII to factor IXa or phospholipids. Thus, the antibody disclosed in Scandella is an inhibitor of factor VIII.

In stark contrast, the claimed polypeptide comprises a heavy chain variable part of a human antibody with factor VIII specificity and a light chain variable part of a human antibody. The claimed polypeptide binds to factor VIII and interferes with the binding of factor VIII

inhibitors to factor VIII. Thus, the claimed polypeptide is an inhibitor of a factor VIII inhibitor. There is no disclosure or suggestion in Scandella of a polypeptide capable of interfering with the activity of factor VIII inhibitors, as is presently claimed.

Accordingly, the claimed invention is not anticipated by Scandella. Therefore, applicants respectfully request that the rejection under 35 U.S.C. §102(b) over Scandella be reconsidered and withdrawn.

Claims 17-18, 60-64, 66, 69, 70-73 and 76-79 were rejected under 35 U.S.C. §102(b) for allegedly being anticipated by Davies (Throm. Haemostas. Supplement 2352, 1997). According to the examiner, Davies teach eight human VIII specific scFvs selected by panning on immobilized rFVIII. Thus, the examiner contends that the claimed invention is anticipated by Davies.

Applicants respectfully disagree. Davies et al. discloses the isolation of eight human factor VIII specific scFv. The abstract merely describes that it is possible to isolate antibodies from the repertoire of patients with antibodies against factor VIII by phage display and express than as scFV fragments.

However, there is no disclosure or suggestion that the scFv fragments disclosed in Davies et al. are capable of interfering with the activity of factor VIII inhibitors, as is required in the claimed invention.

Therefore, the claimed invention is not anticipated by Davies et al. Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. §102(b) over Davies et al. be reconsidered and withdrawn.

Claims 85-86 were rejected under 35 U.S.C. §103(a) for allegedly being obvious over Fijnvandraat et al., Scandella or Davies et al. in view of Marks et al. The examiner states that the

disclosure of the primary references of Fijnvandraat et al., Scandella or Davies et al. have been discussed, supra.

The examiner states that the claimed invention differs from the disclosures of the primary references only by the recitation of a method for producing and isolating a polypeptide antibody in claims 85-86. Thus, the examiner cites Marks et al.

According to the examiner Marks et al. teach a method of producing a recombinant polypeptide antibody. Therefore, the examiner contends that it would have been obvious to one of ordinary skill in the art to make the polypeptide antibody taught by Fijnvandraat et al., Scandella or Davies et al. using the methods and host cells as taught by Marks et al.

Applicants respectfully disagree. As discussed above, nowhere in Fijnvandraat et al., Scandella or Davies et al. is there any disclosure or suggestion of a polypeptide that is capable of specific binding to factor VIII and interference with the activity of factor VIII inhibitors, and that comprises a heavy chain variable part of a human antibody with factor VIII specificity and a light chain variable part of a human antibody.

Marks et al. merely discloses general techniques for producing recombinant polypeptide antibodies. Thus, the combination of Fijnvandraat et al., Scandella or Davies et al. in view of Marks et al. does not result in the claimed invention.

Accordingly, the claimed invention is not obvious over Fijnvandraat et al., Scandella or Davies et al. in view of Marks et al. Applicants respectfully request that the rejection of the claims under 35 U.S.C. §103(a) be reconsidered and withdrawn.

Claim 69 was rejected under 35 U.S.C. §103(a) for allegedly being obvious over Fijnvandraat et al. or Schandell in view of Bird et al. (1988). Applicants have cancelled claim 69. Therefore, the rejection is moot and should be withdrawn.

Claims 20 and 81 were rejected under 35 U.S.C. §103(a) for allegedly being obvious over Davies et al. in view of U.S. Patent No. 4,731,245. The examiner states that the teachings of Davies et al. have been discussed, supra. The examiner states that the claimed invention differs from Davies et al. only by the recitation of a composition with a pharmaceutically acceptable carrier.

Thus, the examiner cites the `245 patent. According to the examiner, the `245 patent teaches a composition comprising an antibody as the active ingredient in association with a pharmaceutically acceptable carrier. Therefore, the examiner contends it would have been obvious to formulate the antibody fragments taught by Davies et al. in a composition with a pharmaceutically acceptable carrier as taught in the `245 patent.

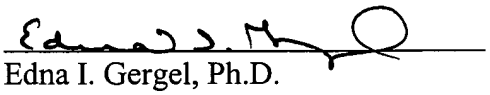
Applicants have cancelled claim 81. With respect to claim 20, the claim is directed to a pharmaceutical composition comprising a polypeptide according to claim 17 or 18. Applicants have provided arguments to refute the rejection of claims 17 and 18 over Davies et al. (see above). Therefore, claim 20 is patentable over Davies et al. at least for the same reasons that claims 17 and 18 are patentable.

Further, the disclosure of the `245 patent merely discloses an antibody against a Streptococcus organism in a pharmaceutical carrier.

Therefore, the combination of Davies et al. and the `245 patent does not result in the claimed invention. Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. §103(a) be reconsidered and withdrawn.

For all of the above reasons, allowance of the pending claims is earnestly requested. If the examiner has any questions regarding this amendment, the examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



Edna I. Gergel, Ph.D.
Registration No: 50,819
Agent for Applicants

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791-4407
Tel. (516) 822-3550
Fax. (516) 822-3582

191352_1